Advances in Therapeutics for Parkinson's Disease

Nonprofit Roundtable

May 3, 2023

Virtual Meeting

Draft May 15, 2023

This meeting summary was prepared by Rose Li and Associates, Inc., under contract to the National Institute for Neurological Disorders and Stroke (NINDS). The views expressed in this document reflect both individual and collective opinions of the meeting participants and not necessarily those of NINDS. Contributions to this meeting summary by the following individuals are gratefully acknowledged: Octavia Martin, Nancy Tuvesson.

Executive Summary

On May 3, 2023, the National Institute of Neurological Disorders and Stroke (NINDS) held the second in a series of roundtable discussions aimed at identifying challenges and opportunities for Parkinson's disease (PD) target validation and therapeutics development. These roundtables will convene industry partners, nonprofit funders, academic researchers, and people with lived experience of PD, and the perspectives shared during these discussions will inform a workshop and white paper focused on barriers to preclinical development of PD therapeutics.

The second Advances in Therapeutics Development for PD roundtable was attended by nonprofit funders and people with lived experience of PD. Topics highlighted by this stakeholder group included the need for (1) patient engagement in PD research and research training, (2) additional disease mechanisms research and development of interventions for nonmotor PD symptoms, (3) diversification of clinical trial populations and standardization of primary endpoints, and (4) multidisciplinary collaboration at each stage of PD therapeutics research and development.

Challenges in Parkinson's Disease Therapeutics Development

Major challenges for the development of effective PD therapeutics include difficulties validating therapeutic targets in clinical trials, lack of research and interventions targeting nonmotor PD symptoms, and incomplete understanding of PD pathophysiology.

Many potentially viable therapeutics may fail at the clinical stage of development because of inadequate clinical trial design. PD clinical trials often have small and homogeneous samples, short duration, and variable primary endpoints that make interpretation and replication of research findings difficult. More research is needed focusing on the development of robust biomarkers that can be used to harmonize clinical trial populations and facilitate the testing of therapeutics and interventions at specific disease stages. In addition, clinical trials should enroll more women and racial/ethnic minorities, groups that may be uniquely affected by PD in ways that are significantly understudied. Some studies suggest, for example, that hormonal fluctuations across the lifespan may affect PD progression and necessitate changes in disease management during menstruation, pregnancy, and menopause. Certain therapeutic targets may not be relevant for all ethnicities, and more research is needed to understand how those targets contribute to disease progression in the groups for which they are relevant.

PD therapeutics development is not only limited by clinical trial design but also by the narrow scope of therapeutic targets. Most PD clinical trials test only motor symptom endpoints, despite many PD patients reporting that symptoms such as hallucinations, pain, and gastrointestinal issues greatly affect their quality of life. In addition, survey data show that many patients with early-stage PD are more afraid of developing PD dementia or psychosis than they are of developing advanced motor symptoms during later disease stages. In order to effectively treat PD and improve patients' quality of life, more therapeutics are needed that target nonmotor symptoms. Moreover, because the prevalence of nonmotor symptoms among PD patients and

dopamine replacement therapy fails to address these symptoms, disease mechanisms other than dopamine depletion should be investigated.

Areas for Improving Parkinson's Disease Therapeutics Development

To facilitate the progression of therapeutics from preclinical to clinical development, patients should be engaged in all stages of PD research and research training. Multiple nonprofit organizations funding PD research encourage interactions between their grantees and patient advocates or Scientific Advisory Board members with lived experiences of PD. Some organizations even provide travel grants for early-career PD researchers to present at research conferences and discuss their findings with PD patients in attendance. Patient feedback can be informative and motivational for all investigators studying PD, ranging from basic scientists to clinical researchers. Multiple nonprofit organizations require grant applicants to specify how individuals with PD contributed to their grant applications, and it may also be useful for information published on ClinicalTrials.gov to specify how patient advocates contributed to trial development.

In addition to patient engagement, collaborative efforts among researchers and between industry, nonprofit, and academic stakeholders are needed to accelerate the identification of disease-modifying therapeutic targets. Because PD lies on a neurodegenerative disease spectrum, PD researchers should regularly communicate with stakeholder groups focused on other diseases such as progressive supranuclear palsy, Lewy body dementia, Alzheimer's disease, Huntington's disease, and multiple sclerosis. Furthermore, partnerships between academic researchers and technology companies could lead to the creation of innovative interventions that apply to a variety of neurological conditions and disabilities.

Small nonprofit organizations are often best suited to fund the unique research areas that may uncover novel disease mechanisms. However, given the expenses associated with pharmaceutical research, some nonprofit organizations may wish to collaborate with pharmaceutical or biotechnology companies to fund the creation of new PD therapeutics. Furthermore, nonprofit and patient advocacy organizations could work together to insist that regulatory agencies allow disease-modifying treatments to be approved earlier with more reliance on biomarker data and fewer requirements for time-consuming and expensive trials.

Necessities for multidisciplinary collaboration and efficient therapeutics development include data accessibility and data sharing. However, pharmaceutical and biotechnology companies are often unwilling to share or publish their data. Some nonprofit organizations are considering requiring grantees, including those from industry, to post some of their data on open-data repositories. However, instead of simply depositing data into repositories, researchers should annotate their data to make it accessible to other researchers with different scientific backgrounds and experience levels.